CADTH Optimal Use Report

Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients: Recommendations

Recommendations Report

February 2016
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBREVIATIONS</td>
<td>IV</td>
</tr>
<tr>
<td>RECOMMENDATIONS IN BRIEF</td>
<td>1</td>
</tr>
<tr>
<td>Technology</td>
<td>1</td>
</tr>
<tr>
<td>METHODS</td>
<td>2</td>
</tr>
<tr>
<td>DETAILED RECOMMENDATIONS</td>
<td>2</td>
</tr>
<tr>
<td>Rationale</td>
<td>2</td>
</tr>
<tr>
<td>Considerations</td>
<td>3</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>4</td>
</tr>
<tr>
<td>Research questions</td>
<td>4</td>
</tr>
<tr>
<td>SUMMARY OF THE EVIDENCE</td>
<td>5</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>5</td>
</tr>
<tr>
<td>Economic Evidence</td>
<td>6</td>
</tr>
<tr>
<td>Patient Preference and Experience Evidence</td>
<td>7</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>8</td>
</tr>
<tr>
<td>APPENDIX 1: HTERP</td>
<td>10</td>
</tr>
</tbody>
</table>
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<td>ELR</td>
<td>external loop recorder</td>
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<tr>
<td>ESUS</td>
<td>embolic stroke of undetermined source</td>
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<tr>
<td>HTA</td>
<td>health technology assessment</td>
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<td>HTERP</td>
<td>Health Technology Expert Review Panel</td>
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<tr>
<td>ILR</td>
<td>implantable loop recorder</td>
</tr>
<tr>
<td>MCOT</td>
<td>mobile cardiac outpatient telemetry</td>
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<tr>
<td>OAC</td>
<td>oral anticoagulants</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS IN BRIEF

Ischemic stroke is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart.\(^1\) Transient ischemic attacks (TIAs) are neurological deficits lasting less than 24 hours, caused by cerebral ischemia.\(^2\) Atrial fibrillation (AF), a type of cardiac arrhythmia,\(^3\) may result in stasis or pooling of the blood in the left atrial appendage of the heart, which can lead to thrombosis formation and subsequent embolization to the brain or to a peripheral arterial site.\(^1\) Patients with AF but no history of stroke have a stroke risk of 4.5% per year, but anticoagulation therapy reduces this risk to 1.4% per year.\(^4\) Roughly 30% to 40% of first-time ischemic strokes are due to an unknown cause,\(^2,5\) and are referred to as an embolic stroke of undetermined source (ESUS).

Long-term electrocardiography (ECG) monitoring using outpatient cardiac monitoring devices can identify occult AF that is undetectable by other means. To this end, outpatient cardiac monitoring devices providing increased mobility for patients and the ability to transmit data wirelessly have been developed, which allow for longer-term surveillance outside the hospital setting. These devices include ambulatory Holter monitors, external loop recorders (ELRs), mobile cardiac outpatient telemetry (MCOT) devices, and implantable loop recorders (ILRs).\(^2\)

To inform decision makers about the appropriate use of outpatient cardiac monitoring devices in patients who have experienced a stroke or TIA, CADTH conducted a health technology assessment (HTA)\(^6\) on the clinical effectiveness and cost-effectiveness of cardiac monitoring devices in outpatient stroke or TIA patients. Patient perspectives and experiences regarding the value and impact of outpatient AF cardiac monitoring devices were also considered.

For discharged ischemic stroke or TIA patients who have received no prior in-hospital continuous cardiac monitoring, HTERP recommends 7 days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or external loop recorder.

Technology

Ambulatory Holter monitors typically have three to eight leads connected to a patient’s chest, and a small monitor that is carried in a pouch around the neck or waist.\(^7\) Data from the monitor’s continuous recording are stored, then transmitted via the Internet. Patients are also able to mark symptomatic events.\(^7\) Holter monitors can record up to 72 hours, depending upon the particular device.

ELRs use chest electrodes or a wrist band to continuously monitor cardiac activity. The recording is activated by previously set heart rate ranges or by the patient, using a hand-held activator.\(^8\) The devices can be worn up to 30 days, but are only capable of storing approximately 10 minutes of activity. The data is transmitted to the physician or data centre via telephone.\(^7\)
ILRs operate similarly to ELRs, but are implanted subcutaneously, through a small incision. They automatically record cardiac arrhythmias or can be patient-activated. The devices can remain implanted for about three years and are removed afterward. Storage capacity is up to 50 minutes.

MCOT devices use three or four electrodes to monitor cardiac activity. The data is sent to the patient’s cellphone, then sent in real time to a data centre. The sensor can store from six hours to 30 days of data and the device is worn for up to 30 days.

**METHODS**

CADTH conducted an HTA on the clinical effectiveness, cost-effectiveness and related patient preferences and experiences of outpatient cardiac monitoring devices in patients who have experienced a stroke or TIA. HTERP developed recommendations on the appropriate use of outpatient cardiac monitoring devices based on the evidence presented in the HTA report. HTERP members reviewed the evidence, discussed all elements of the HTERP deliberative framework, and developed a consensus based recommendation through discussion and deliberation. Additional information on the HTERP process are found on the HTERP page of the CADTH website: [https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel](https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel)

**DETAILED RECOMMENDATIONS**

The objective of these recommendations is to provide advice for Canadian health care decision makers about the appropriate use of outpatient cardiac monitoring devices. These recommendations are relevant for ischemic stroke or TIA patients, including but not limited to those with ESUS, who have received no prior in-hospital continuous cardiac monitoring (e.g. in-hospital Holter, continuous in-patient cardiac telemetry, or continuous ECG monitoring).

**For discharged ischemic stroke or TIA patients who have received no prior in-hospital continuous cardiac monitoring**, HTERP recommends 7 days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or external loop recorder.

**Rationale**

- There is a substantial increase in diagnostic yield of AF when monitoring for greater than 24 hours.
- In relatively healthy patients who are eligible for oral anticoagulants (OACs) if diagnosed with AF and who did not receive in-hospital continuous monitoring (patients who received ECG only), seven days of monitoring with ambulatory Holter or ELR is likely to identify a substantial number of patients with AF at an acceptable incremental cost compared to standard of care (defined as providing 24-hour monitoring to 60% of patients).
- Continuous outpatient monitoring for patients receiving prior in-hospital continuous cardiac monitoring (e.g. in-hospital Holter, continuous in-patient cardiac telemetry, or continuous ECG monitoring) is unlikely to be cost effective as the incremental diagnostic yields may not be sufficient to compensate for the substantial increase in testing costs.
In addition to ischemic stroke or TIA patients, the overall findings suggest that outpatient cardiac monitoring for the detection of AF is warranted in patients with ESUS as this subpopulation also demonstrated high diagnostic yields.

Most patients perceive ambulatory Holters and ELRs as easy to use and relatively comfortable.

**Considerations**

Canadian Cardiovascular Society Guidelines recommend a minimum 24 hours of ECG in-hospital monitoring for the detection of AF, yet standard practice varies across Canada. Findings from the clinical review concluded that longer duration of monitoring appears to result in a greater likelihood of detecting AF, with substantial increases when monitoring for greater than 24 hours. With few comparative studies, there was uncertainty regarding the relative clinical effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke or TIA patients compared with each other and with no monitoring. In addition to ischemic stroke or TIA patients, the overall findings suggest that outpatient cardiac monitoring for the detection of AF is warranted in patients with ESUS as this subpopulation also demonstrated high diagnostic yields. Interpretation of clinical findings was limited by the significant amount of clinical and statistical heterogeneity between studies in regards to different patient populations, duration of monitoring and definitions of AF.

While the optimal duration of outpatient cardiac monitoring remains uncertain, 7-day cardiac monitoring was found to be cost-effective in relatively healthy post-stroke and TIA patients who have not otherwise been evaluated using continuous monitoring technologies when compared to standard of care (defined as providing 24-hour monitoring to 60% of patients). Differences in billing codes for these devices may differ between jurisdictions and should be considered. For example, serial testing conducted for seven days using individual one-day billing codes may no longer be cost effective. Seven day monitoring can be performed using Holter or ELR depending on local costs and availability. ELRs are not currently available in all Canadian jurisdictions. Outpatient monitoring with ILR up to three years compared with standard practice (defined as 38% of patients receiving ECG or 24-hour Holter monitoring within six months) was not cost effective among cryptogenic stroke patients receiving prior in-hospital ECG or 24-hour Holter monitoring. The economic review also suggested that 30-day ELR is unlikely to be cost effective compared with 24-hour Holter. Interpretation of the economic models is limited as many comparisons of interest were not evaluated, there were many simplifying structural assumptions, and models considered patients at average risk after stroke or TIA.

There was insufficient evidence in the clinical review to suggest any differences in safety (i.e., stroke recurrence and stroke/all-cause mortality) between the outpatient devices. The review of patient preferences and experiences was likewise limited with insufficient evidence, however concluded that overall, most patients perceive ambulatory Holters and ELRs as easy to use and relatively comfortable. Interpretation of the patient preference and experience evidence is further limited by the inclusion of a broader patient population including all patients who have used outpatient monitoring devices for any indication. No Canadian studies were found, and no studies used validated outcome measures. The systematic assessment of compliance was outside the scope of this review. However, HTERP clinical experts suggested there may be additional compliance issues when monitoring for greater than 30 days compared with a 7-day monitoring device.

DRAFT: Recommendations for Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients
No studies were identified pertaining to the ethical, legal, and social implications associated with outpatient cardiac devices for AF monitoring. As well, no clinical studies addressed the implementation considerations (technical requirements, staffing, training, and accreditation) for outpatient monitoring devices for AF monitoring. Privacy issues regarding the transmission of personal information should be considered. In comparison with 24-hour monitoring, the recommendation of 7-day monitoring with ELR or ambulatory Holter may require added resources including additional cardiac monitoring devices and clinical personnel.

With further research, emerging technologies such as intermittent handheld ECG monitors, which were outside the scope of this report, may prove to be a cost-effective option for outpatient cardiac monitoring in the future. Furthermore, additional research on the optimal duration of monitoring is needed. Shorter or longer duration of monitoring may be clinically appropriate for certain patient cohorts based on their personal risks, baseline health and comorbidities, and preferences regarding testing. While HTERP does not recommend the use of outpatient cardiac monitoring beyond seven days with an ambulatory Holter or ELR, or any outpatient monitoring with ILRs and MCOTs, shared physician-patient decision making should be considered in this context.

BACKGROUND

In-patient cardiac monitoring following a stroke or TIA alone captures a fraction of occult AF cases and substantial evidence suggests that the detection rate increases with prolonged surveillance time.\textsuperscript{2,12,13} An analysis of the clinical effectiveness, cost-effectiveness, and review of patient preference and experiences was conducted to inform decisions for adopting a policy of discharging stroke patients with outpatient cardiac monitoring devices.

The clinical, economic, and patient preference and experience evidence used for developing this guidance was derived from the CADTH HTA: Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients.\textsuperscript{6}

Research questions

1. What is the clinical effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke and/or TIA patients:
   - compared with each other
   - compared with no monitoring?

2. What is the cost-effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke and/or TIA patients:
   - compared with each other
   - compared with no monitoring?

3. What are the perspectives and experiences of adults and their caregivers who have made a decision regarding the use of outpatient cardiac monitoring devices regarding the value and impact of these devices for atrial fibrillation monitoring on their health, health care, and quality of life?
SUMMARY OF THE EVIDENCE

Clinical Evidence

The systematic review of the clinical effectiveness literature assessed the proportion of post-stroke and/or TIA patients diagnosed with AF by four different outpatient cardiac monitoring devices in 36 studies. Individual study results were presented and synthesized narratively. Pooling estimates of the proportion of patients diagnosed with AF post-stroke or TIA for each device through meta-analysis was not appropriate given the considerable amount of statistical and clinical heterogeneity.

Evidence has shown that prolonged surveillance using outpatient monitoring devices following patient discharge is able to capture more AF cases in comparison with shorter in-hospital cardiac monitoring.\textsuperscript{2,12,13} This was generally reflected in our findings as there was a substantial increase in diagnostic yield when monitoring for greater than 24 hours. Specifically, patients were monitored for the greatest duration with ILRs (ranging between 105 days and 569 days) and demonstrated greater numerical diagnostic yields than monitoring patients for shorter durations with other devices (i.e., ambulatory Holter, MCOTs, and ELRs). For example, one RCT\textsuperscript{3} comparing longer monitoring using ILR to standard of care (defined as conventional follow-up with additional ECG monitoring beyond 24 hours per the hospitals' procedures) demonstrated a statistically significant greater diagnostic yield. However, while monitoring patients beyond 30 days demonstrated greater diagnostic yield compared with less than 30 days, improvements were modest and may be achieved by changes in monitoring technologies alone. A prospective cohort study comparing ILR to ambulatory Holter reported that ILR demonstrated a three times greater diagnostic yield when evaluated at 7 days.\textsuperscript{14}

One RCT comparing MCOTs to no monitoring did not detect AF in either group and therefore demonstrated no differences between interventions. However, this was a pilot study reporting only the first 20 patients in each group.

Studies comparing ELRs to ambulatory Holters contradicted the trends observed in non-comparative cohort studies. In the cohort studies, patients were mostly monitored for greater duration with ELRs (ranging between 3 days 30 days), however there was no clear improvement in diagnostic yield compared with ambulatory Holters (ranging from 1 day to 28 days). When compared directly in two RCTs.\textsuperscript{15,16} ELRs demonstrated a statistically superior diagnostic yield compared with ambulatory Holters, though the duration of monitoring was longer with ELR than ambulatory Holter (7 to 30 days versus 1 day).

In the ambulatory Holter and ELR studies, there was no pattern observed between diagnostic yield and type of stroke (ESUS exclusively versus all stroke populations). The majority of MCOT and ILR studies (all but one for each) consisted of ESUS patients exclusively. There was no pattern observed between diagnostic yield and duration of monitoring for MCOT, ELR and ILR studies. When comparing studies that used ambulatory Holters, the diagnostic yield generally increased with a greater duration of monitoring (greater than one day). In regards to prognostic factors, there was no pattern observed between diagnostic yield and mean age for ambulatory Holter, MCOT and ILR studies. For ELR studies, diagnostic yield generally increased in studies with a greater mean age. For all devices, no pattern was observed between diagnostic yield and sex.
Longer duration of monitoring appears to result in a greater likelihood of detecting AF, for any definition of AF (paroxysms of any duration vs. at least one paroxysm greater than 30 seconds). There was insufficient evidence to determine how much more common AF detection is with a definition of < 30 seconds vs ≥ 30 seconds because few studies report on the proportion of patients observed to have only paroxysms shorter than 30 seconds. A recent meta-analysis estimated that if AF were defined based on paroxysms of any duration that more than half (56.3%, 95% CI: 37.7-74.0%) of patients would be diagnosed on the basis of paroxysms shorter than 30 seconds. The clinical and prognostic significance of short duration paroxysms is unknown and may become important to patients and clinicians as more patients are identified in this group through expanded monitoring. With few comparative studies, there was insufficient evidence to distinguish the clinical effectiveness between devices or the optimal duration of long-term monitoring.

**Economic Evidence**

The economic findings were based on three individual RCTs, in which it was found that 7-day cardiac monitoring in patients with a very recent history of stroke or TIA who did not receive in-hospital continuous monitoring (patients who received ECG only) is likely to identify a substantial number of patients with AF at an acceptable incremental cost compared to standard practice. The other two longer-term monitoring strategies, including 30-day ELR or ILR are unlikely to be cost effective in the patient cohorts studied by Gladstone et al. or Sanna et al. Both of these cohorts were selected as higher-risk cohorts based on their stroke type, but both cohorts had already undergone at least 24-hours of continuous in-hospital monitoring. As a result, the incremental diagnostic yields observed in these studies were not sufficient to compensate for the substantial increase in testing costs incurred for all patients. As technologies such as ELRs decrease in cost, longer term monitoring may become cost effective in target populations. ILRs are unlikely to be cost effective for the purpose of investigating atrial fibrillation in a post-stroke population.

Longer term monitoring, such as 30-day event loop recording or implantable cardiac monitoring, in patient cohorts similar to those studied by Gladstone et al. or Sanna et al. had ICERs greater than $100,000 per QALY gained and are therefore unlikely to be cost effective in Canada. Both of these cohorts were selected as higher-risk cohorts based on their stroke type, but both cohorts had already undergone at least 24-hours of continuous monitoring. As a result, the incremental diagnostic yields were not sufficient to compensate for the substantial increase in testing costs incurred for all patients. As technologies such as external loop recorders decrease in cost, they may become cost effective technologies in target populations. Implantable loop recorders are unlikely to be cost effective for the purpose of investigating AF in a post-stroke population.

Cardiac monitoring after stroke or TIA for the investigation of AF can be cost effective. To ensure cost effective monitoring, the incremental cost compared to standard practice must be relatively small, the diagnostic yield must be substantial, the patient cohort must be relatively healthy for a post-stroke patient, and the initiation of OACs in newly diagnosed patients must be high. To achieve a high diagnostic yield, the patient cohort must be one with a high expected prevalence of AF based on their medical history, type of stroke and stroke symptoms, recently discharged after their stroke and having had few investigations for atrial fibrillation in-hospital.
Patient Preference and Experience Evidence

A review of nine studies that included data regarding patient perspectives and experiences suggests that most patients perceive outpatient cardiac monitoring devices to be comfortable and easy to use, and satisfaction with outpatient cardiac monitoring is high. Patient preferences for one device type over another appear to be based on participant perceptions of overall comfort and ease of use, related to such attributes as material, comfort and fit. Experienced side effects include skin irritation (e.g., itching, bleeding, inflammation), pressure and difficulty bathing. It is unclear whether outpatient monitoring has any impact on quality of life or anxiety.

If outpatient monitoring is to be effective, monitoring devices need to be comfortable, easy to use and with few painful side effects so that people are more likely to comply with monitoring recommendations. While the systematic assessment of compliance was outside the scope of this review, the results suggest that negative side effects might result in reduced compliance. This suggestion is supported by results of studies included in the accompanying clinical review, which report adverse skin reactions, discomfort, irritation and inflammation as reasons for non-compliance with ELRs and ambulatory Holters and refusal to provide consent for implantation of an ILR.
REFERENCES


APPENDIX 1: HTERP

HTERP consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, four expert members were appointed; their expertise included internal medicine, clinical chemistry, pathology, and family medicine. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available at www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel.

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Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.